REMARKS

The Office Action dated June 29, 2005, has been received and reviewed. Claims 52-84 are pending in this application. Claims 1-4, 8-14, 20-27 and 49-51 have been canceled without prejudice or disclaimer. Any canceled subject matter not presently claimed is reserved for filing in one or more continuing applications. Claims 1-4, 8-14, 20-27 and 49-51 were rejected in this Office Action. Applicants respectfully request reconsideration of the application as amended herein and in view of the remarks below and on Dr. Adler's declaration.

Applicants and their attorneys would like to thank Examiner Haddad and his supervisor, Supervisory Patent Examiner Chan, for kindly granting an interview on October 5, 2005.

I. Claim Amendments

Independent claims 52, 64 and 76 have been amended to recite "a pharmaceutical composition comprising a MANS peptide consisting of an amino acid sequence of SEQ ID NO: 1" which is supported by the specification and claims. Claim 64 also is supported by previous claim 12 and in paragraph [0039] of the specification. Claims directed to disease groups and specific disease are supported by the original claims and the specification in paragraphs [0041] and [0042]. Claims 55, 68 and 76 are supported in the specification in paragraphs [0012] and [0042]. Claims 61, 70 and 82 are supported by paragraph [0043]. The remaining claims are supported in the specification or original claims as filed. The new set of claims have been provided to more specifically claim applicants' invention.

II. Claims Rejections – 35 U.S.C. § 112, First paragraph

Claims 1-4, 8-14, 20-27, and 49-51 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse these rejections and

request reconsideration based on the presently pending set of claims and for the reasons enumerated below.

Written Description

Applicants note that the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (MPEP §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Furthermore, the test for whether or not the enablement requirement has been met involves determining whether or not practice of the invention as claimed involves "undue experimentation". It has long been settled that "the key word is 'undue', not 'experimentation'". *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). Applicants submit that the current technology requires routine effort, and not undue experimentation. However, in an effort to expedite prosecution, Applicants have amended the independent claims to recite that a pharmaceutical composition comprising a MANS peptide consisting of an amino acid sequence of SEQ ID NO: 1 is administered in the claimed method. In view of this amendment, it is requested that the rejection based on the alleged lack of written description for an active MANS fragment be withdrawn.

Enablement

The Examiner states that the specification does provide "some guidance with respect to neutrophils" that previously pending claims 49-51 recite reducing/inhibiting an inflammatory mediator but that the specification provides "no working examples to modulate any neutrophils, basophils, eosinophils, monocytes or leukocytes." As pointed out in the last response, Figures 9 and 10 provide *in vitro* evidence of a dose-dependent response where MANS peptide reduces the level of MPO (myeloperoxidase), an inflammatory mediator, in activated neutrophils and Figures 11 to 15 provide data that MPO secretion can be stimulated in human and canine neutrophils. Applicants refer the Examiner to the very detailed discussion of the results and significance of the data provided in Figures 9-15 of the specification proved in the previous response.

Applicants again refer the Examiner to MPEP § 2164.02 (pages 2100-187 and 188 of the MPEP, Rev. 2, May 2004), which discusses the significance of working examples and

particularly the correlation of *in vitro/in vivo* models. The paragraph bridging pages 2100-187 and 188 states that an *in vitro* example in the specification constitutes a "working example" if that example "correlates" with a disclosed or claimed method of the invention. Applicants submit that the claims are directed to administering MANS peptide with a specific sequence to a subject to block the release of inflammatory mediators and that MPO is an inflammatory mediator and neutrophils are inflammatory cells. Applicants further submit that neutrophils are recognized as being correlated to inflammation and applicants refer the Examiner to Dr. Kenneth Adler's declaration, attached as Appendix A, and particularly to paragraphs 6.–9, in which Dr. Adler discusses how *in vitro* studies with granulocytes, which includes neutrophils and eosinophils, are predictive of the outcome of inflammatory diseases *in vivo*. In paragraphs 8 and 9 of his declaration, Dr. Adler provides two publications where granulocytes are used in *in vitro* studies and relied upon as predictive of *in vivo* outcome by the authors. Applicants submit that these publications are indicative that one skilled in the art would accept the *in vitro* model of studying stimulated neutrophils as reasonably correlated to inhibiting the release of an inflammatory mediator in a subject. "A rigorous or an invariable exact correlation is not required (MPEP § 2164.02, page 2100-188, first column). Applicants note that if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless there is evidence that the model does not correlate. *See*, M.P.E.P. § 2164.02; *See also, In re Brana* 51 F.3d 1560, 1566. Therefore, Applicants submit that Dr. Adler's comments and the provided publications provide evidence that the enablement standard is satisfied in the present application because the *in vitro* experiments do provide evidence that are predictable and relied upon by skilled persons that can be reliably extrapolated to the behavior of these cells *in vivo*. Accordingly, Applicants respectively request reconsideration based upon the above arguments and pending set of claims, and request withdrawal of the rejections to the pending claims.

III. Claims Rejections – 35 U.S.C. § 103(a)

A. Adler et al (CHEST. May, 2000)

Claims 1-4, 8-14, 20-27, 49 and 50 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Adler et al (CHEST. May, 2000), (hereinafter "the Adler abstract").

Applicants traverse this rejection for the reasons set forth below and those provided in Dr. Adler's declaration (Appendix A).

To establish a prima facie case of obviousness, the prior art reference or references when combined must teach or suggest *all* the recitations of the claim, and there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. § 2143.01, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). To support combining references, evidence of a suggestion, teaching, or motivation to combine must be clear and particular, and this requirement for clear and particular evidence is not met by broad and conclusory statements about the teachings of references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). The Court of Appeals for the Federal Circuit has also stated that, to support combining or modifying references, there must be particular evidence from the prior art as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). Furthermore, as recently affirmed by the Court of Appeals for the Federal Circuit in *In re Sang-su Lee*, a factual question of motivation is material to patentability, **and cannot be resolved on subjective belief and unknown authority**. *See In re Sang-su Lee*, 277 F.3d 1338 (Fed. Cir. 2002). Respectfully, as will be discussed below, the Official Action fails to meet the requirements for a prima facie showing of obviousness under § 103.

The Examiner is erroneously relying on the first sentence of the Adler abstract for motivation to support his position that the claims are obvious over the Adler abstract. Applicants respectfully submit that the sentence "[h]persecretion of mucus contributes to airway inflammation and obstruction in COPD" was not intended to establish a scientific link between mucus secretion and inflammation. Dr. Adler is an expert in the respiratory field, and in his attached declaration, paragraph 3, he explains that there is no direct link between excess mucus and inflammation, and that mucus secretion does not cause inflammation. Dr. Adler qualifies what he meant by this sentence in that excess mucus can, if it allowed to build up, make the airways susceptible to microbial infection, which in turn can possibly result in

inflammation. Dr. Adler makes it clear that mucus secretion and inflammation are two separate processes.

Dr. Adler further states in paragraph 4, a person skilled in the art, such has himself, would not be motivated by his own abstract, to treat inflammation by blocking the release of inflammatory mediators, with a synthetic peptide of the myristic acid containing N-terminal region of MARCKS protein. In paragraph 5 of his declaration, Dr. Adler further supports his position by citing Haile *et al.* which confirms that mucus secretion is not associated with inflammation. Thus, the Adler abstract only discloses mediating mucus secretion with this synthetic peptide and does not suggest that treating or mediating inflammation as suggested by the Examiner.

Additionally, the Adler abstract does not specifically recite that mucus secretion is mediated by the MANS peptide having the sequence of SEQ ID NO:1, as now claimed in all of the presently pending claims. Rather Adler states that mucin hypersecretion was inhibited by a synthetic peptide of the myristic acid containing N-terminal region of MARCKS protein. A skilled person reviewing Adler would not specifically be able to determine that MANS peptide with a specific 24 amino acid sequence was the peptide that was used to mediate mucin secretion. Thus, the Adler abstract does not render the claimed invention obvious.

Further, Applicants submit that if their own application is not enabled, which the Examiner alleges because there are no *in vivo* examples, then to be consistent with that principle, the Adler abstract should also not be considered to be enabled because it does not contain any *in vivo* examples for inhibiting the release of an inflammatory mediator.

As also discussed at the interview, the Adler abstract actually provides a **negative teaching,** for one skilled in the art that would be led away from a therapeutic application of the present invention, particularly for the treatment of lung disease, because the Abstract teaches that the N-terminal region of the MARCKS protein antagonizes UTP.

UTP is well known as a therapeutic compound for treating lung diseases, including "cystic fibrosis, chronic bronchitis, asthma, and bronchiectasis" *See, e.g.,* R. Boucher, *Method of treating lung disease with uridine Triphosphates,* US Patent No. 5,292,498 (abstract; column 3 lines 45-55)(copy submitted concurrently herewith). Given the known

therapeutic activity of UTP, persons of ordinary skill in the art would be reluctant at best to utilize an antagonist thereof as a therapeutic agent, such as for the treatment of lung disease.

Again, Applicants note that the present invention relates to methods of inhibiting **inflammatory mediators released from inflammatory cells** and **not epithelial cells** as recited in the Adler abstract. Applicants submit that it is well known in the art that **epithelial cells and inflammatory mediators are different** from one another. Applicants submit that it is known that a wide variety of agents and inflammatory/humoral mediators can provoke mucin secretion. These include cholinergic agonists, lipid mediators, oxidants, cytokines, neuropeptides, ATP and UTP, bacterial products, neutrophil elastase, and inhaled pollutants. Applicants further note that epithelial cells and inflammatory cells have very different responses to exogenous stimuli and can have different biochemical signaling pathways. Thus, it would not be expected from the Adler abstract that inflammatory cells would behave similarly to epithelial cells. Accordingly, Applicants respectfully submit that the Adler abstract does not teach or suggest the one skilled in the art could inhibit the release of an inflammatory mediator by treatment with MANS peptide as claimed in present application. There is nothing in this abstract, which would make the present invention obvious. Applicants submit that this reference fails to contain any motivation to combine their teachings as required by *In re Sang-su Lee*. Furthermore, even if Adler was combined with another publication, one would not arrive at the present invention as it relates to inflammatory mediators. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection to all of the pending claims because the Adler abstract does not render the claimed invention obvious.

B. U.S Patent No. 6,506,779

Claim 51 also was rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 6,506,779 in view of the Adler abstract. Applicants submit that the '779 patent relates to acetylene derivatives, methods of treatment and pharmaceutical compositions for the treatment of cyclooxygenase mediated diseases. It does not in any way discuss or even contemplate the MANS peptide or a MARCKS related protein. Accordingly, for the reasons stated above and in this section, Applicants submit that the '779 patent and the Adler abstract either alone or in

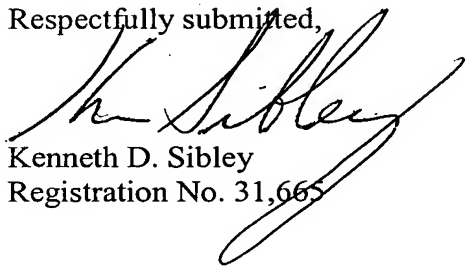
combination fail to contain any motivation to combine their teachings as required by *In re Sang-su Lee*. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection to present Claims 65 and 87.

CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully submitted,



Kenneth D. Sibley
Registration No. 31,665

USPTO Customer No. 20792
MYERS BIGEL SIBLEY & SAJOVEC
Post Office Box 37428
Raleigh, North Carolina 27628
Telephone: 919/854-1400
Facsimile: 919/854-1401